

Definition of molecular interaction networks

To be able to construct and analyze a cellular network, we need to clearly define what we identify as a node and what we represent with an edge.

The nodes and edges have to be at least similar to each other, e.g. represent the same type of cellular component (protein, chemical) or the same type of interaction (mass transfer, regulation).

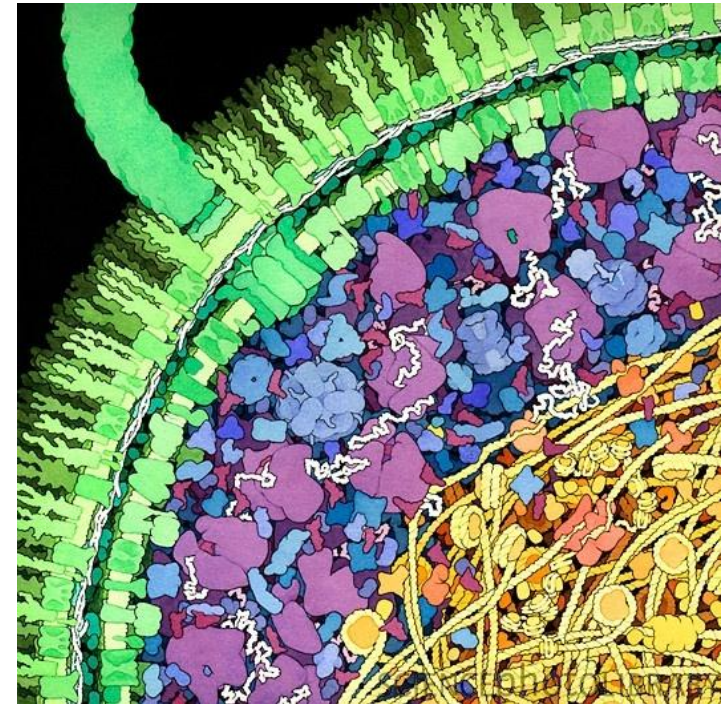
We can, and often need to, define different types of nodes and edges.

A few important biology concepts

- Four basic types of molecules involved in life: small molecules, proteins, DNA, RNA
- A **gene** is a stretch DNA from which a molecular machinery can read information and make a particular type of protein or a few different proteins.
- Protein synthesis has two main stages: **transcription** of DNA into mRNA, **translation** of mRNA into protein.
- Transcription is regulated by transcription factors.
- Biochemical reactions transform reactants (also called substrates) into products and may be catalyzed by **enzymes**.
- The **metabolism** is the biochemical reaction network through which organisms transform nutrients taken from their environment into the molecules necessary for carrying out cellular functions (e.g. ATP).
- The reactants and products of metabolic reactions are called **metabolites**.
- **Receptor** proteins sense molecules in the environment; these molecules are referred to as **ligands** or signals.

Life at the cellular level

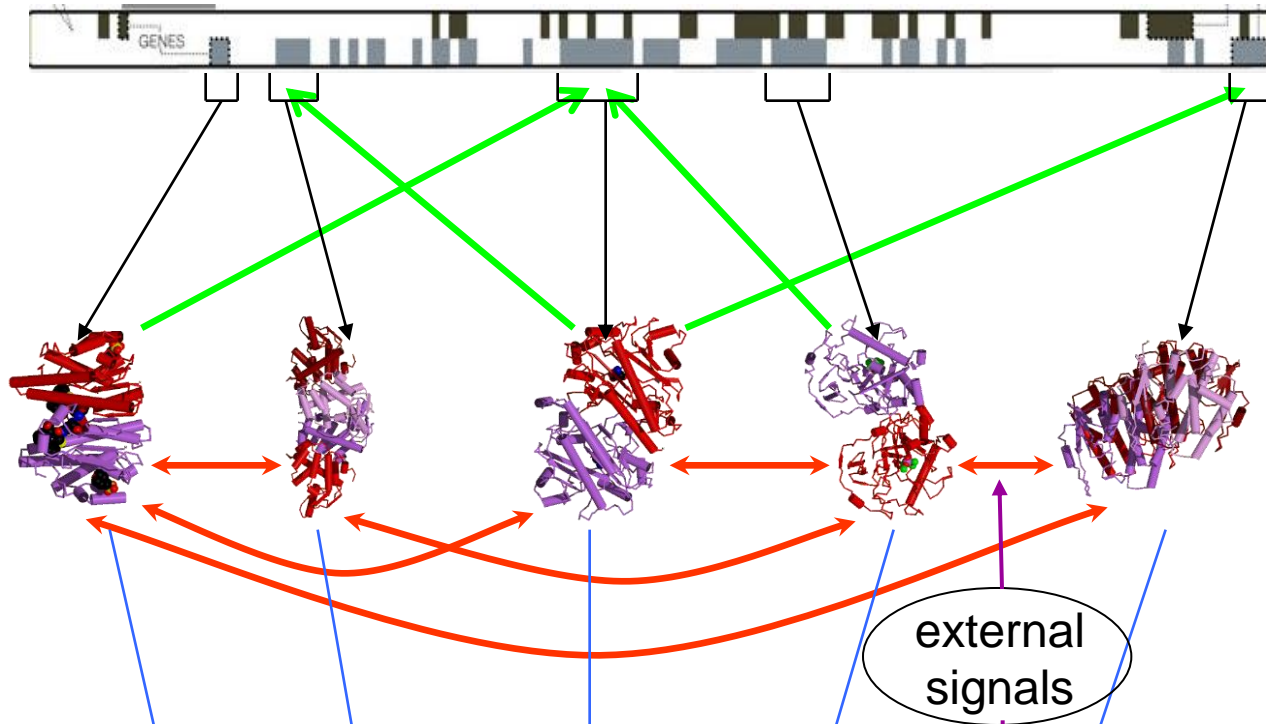
- Cellular functions rely on the coordinated action of interacting components.
- Proteins
 - provide structure to cells and tissues
 - work as molecular motors
 - sense chemicals in the environment (receptors)
 - drive chemical reactions (enzymes)
 - regulate gene expression (transcription factors)
- Interconnections between components are the essence of a living process.



receptor proteins, enzymes,
translation machinery, DNA

David Goodsell/ Science Photo Library

Frequently defined molecular interaction networks



gene regulatory
network

protein-protein
interaction
network

signal transduction
network

bio-chemical
reaction
network

Examples of intracellular networks

1. Protein interaction networks

nodes: proteins

edges: protein-protein interactions (binding), modification of a protein

2. Biochemical reaction networks

nodes:

reactants (substrates) or products of the reactions

enzymes – catalyze the reactions

reactant-enzyme complex (“reaction node”)

edges:

reactions

catalysis (regulation)

Examples of intracellular networks (cont.)

3. Gene regulatory networks

nodes:

gene, mRNA, protein

edges:

transcription, translation, regulation

4. Signal transduction networks

nodes:

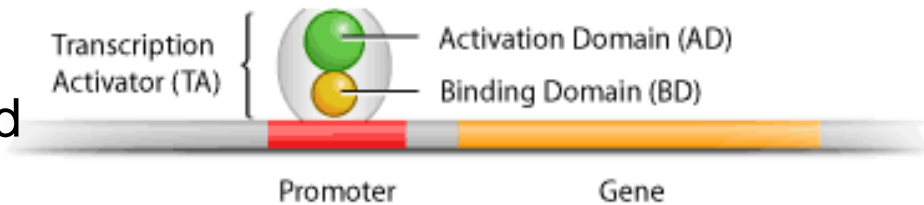
proteins, molecules

edges:

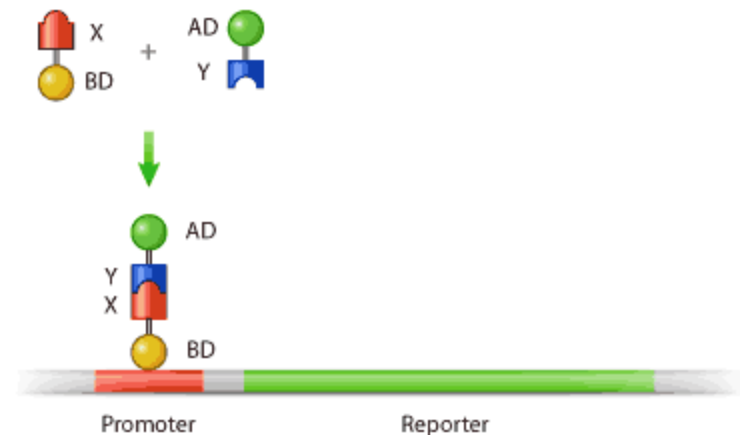
reactions and processes (e.g. ligand-receptor interaction)

Example of high-throughput experimental methods to map interactions

Transcription factors bind to the promoter regions of genes. They have a DNA binding domain and an activation domain.



In the two-hybrid method the two domains are separated, and fused to two proteins. If the two proteins interact by binding, the transcription factor activates the expression of a reporter gene.



Systematic experiments with all proteins in a given organism lead to genome-wide protein interaction maps.

Mapping of cellular interaction networks

Experimental advances allow the construction of genome-wide cellular interaction networks

- Protein networks (interactome):

- Individual studies:

- Uetz et al. 2000, Ito et al. 2001, Krogan et al. 2006, Yu et al. 2008 – *S. cerevisiae*,

- Giot et al. 2003 – *Drosophila melanogaster* , Li et al. 2004 – *C. elegans*

- Rual et al. 2005 - Human interactome

- High throughput methods:

- Co-affinity purification + mass spectrometry

- Yeast two hybrid

- Databases:

- Database of Interacting Protein (DIP), the Biomolecular Interaction Network (BIND), the Munich Information Center for Protein Sequences (MIPS), the Human Protein Reference Database (HPRD), and the Yeast Proteome Database (YPD)

Mapping of cellular interaction networks (cont.)

- Metabolic networks

Experimental methods:

Enzyme characterizations: Protein and DNA microarrays

Metabolite identification (metabolome): isotope labeling

Flux quantification: Mass spectroscopy

Databases: Kyoto Encyclopedia of Genes and Genomes (KEGG), Ecocyc, MetaCyc

- Transcriptional regulatory networks

Individual studies: Shen-Orr et al. 2002 – *E. coli*, Guelzim et al 2002, Lee et al. 2002 - *S. cerevisiae*,

Davidson *et al.* 2002 – sea urchin

Experimental methods: DNA footprinting, chromatin immunoprecipitation (ChIP)

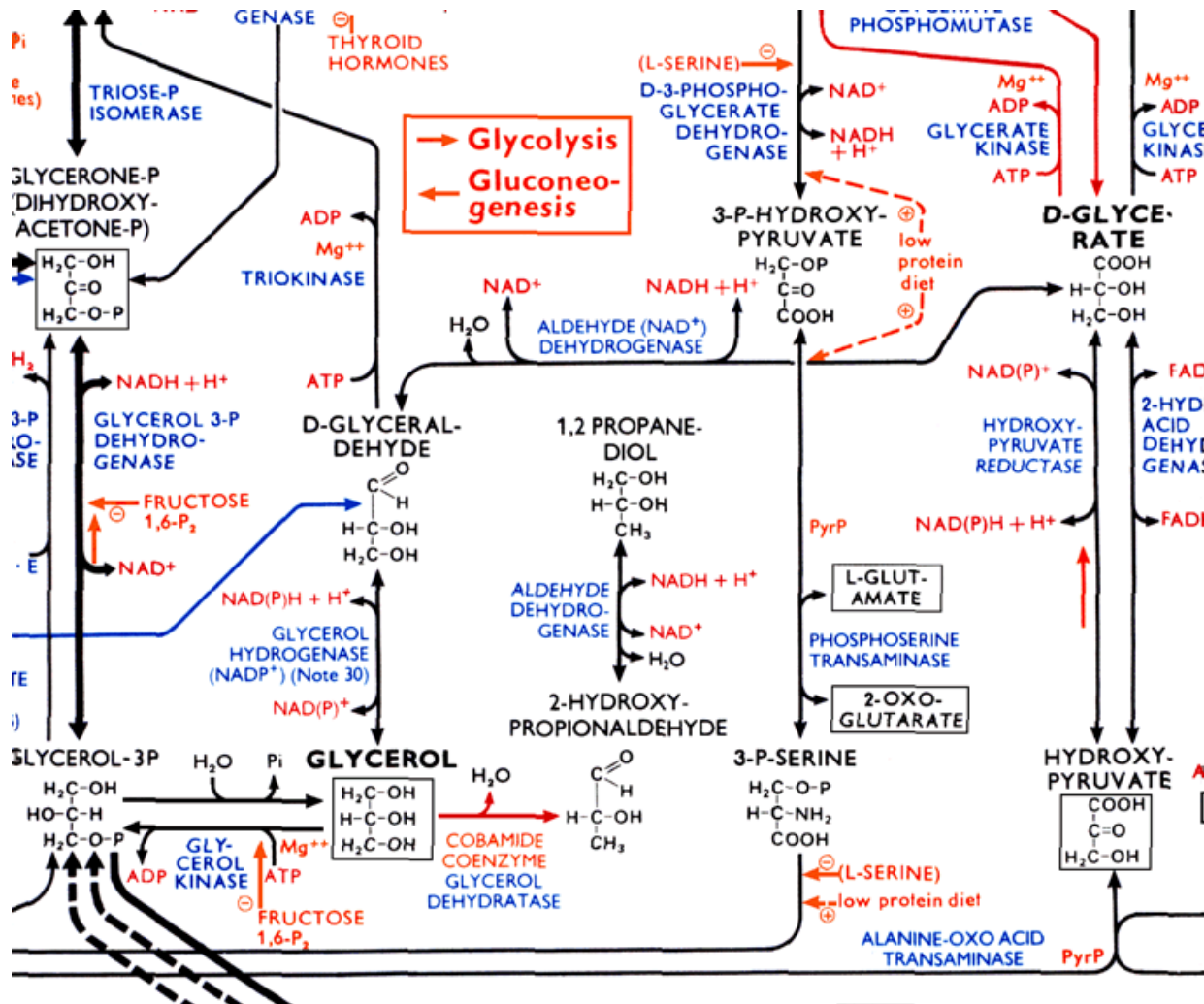
Databases: Transcription Factor Database (TRANSFAC), Regulon Database (RegulonDB), KEGG

- Signal transduction networks

Ma'ayan et al. 2005 – mammalian hippocampal neuron

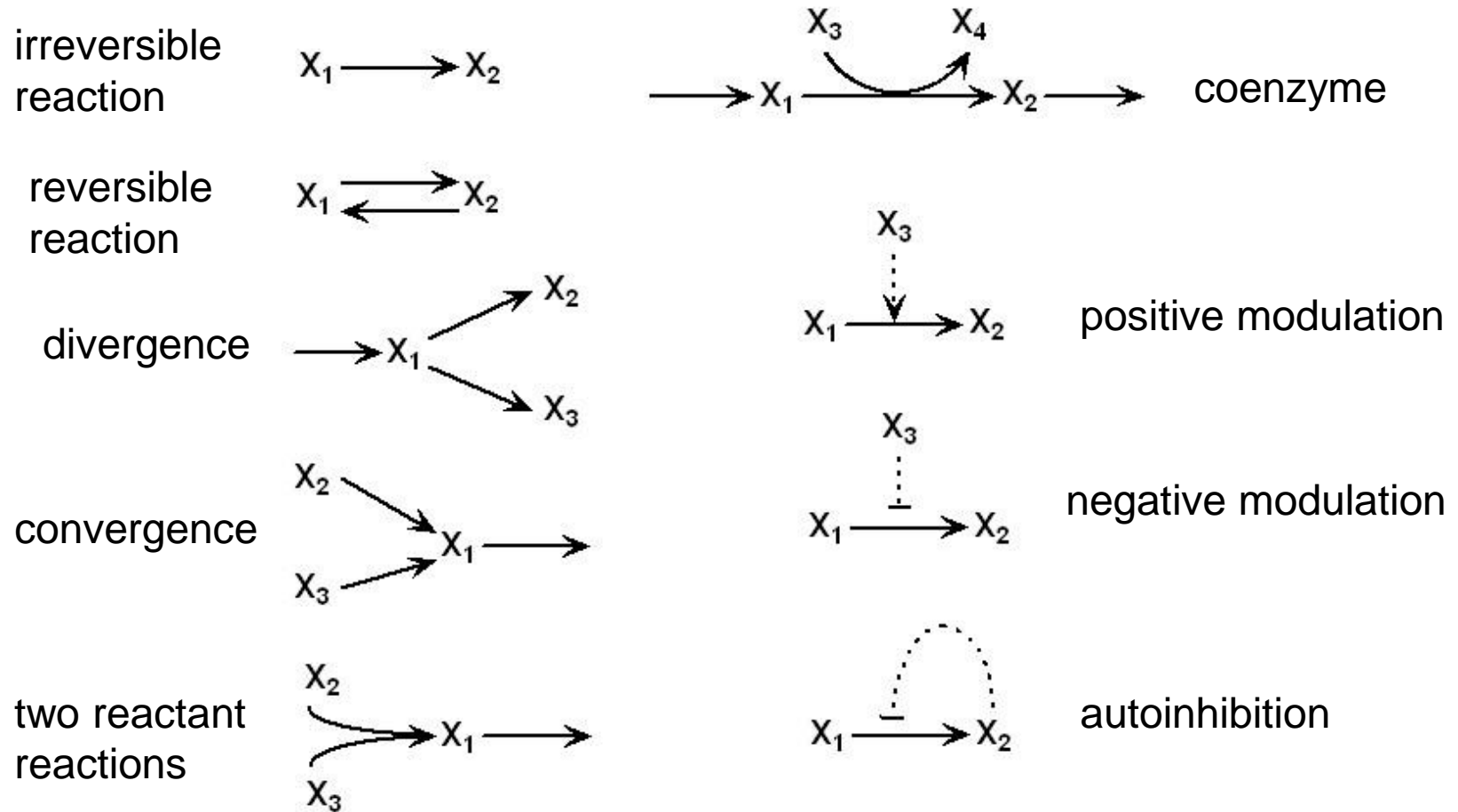
Databases: KEGG, Science STKE

Networks of chemical reactions –usual visualization

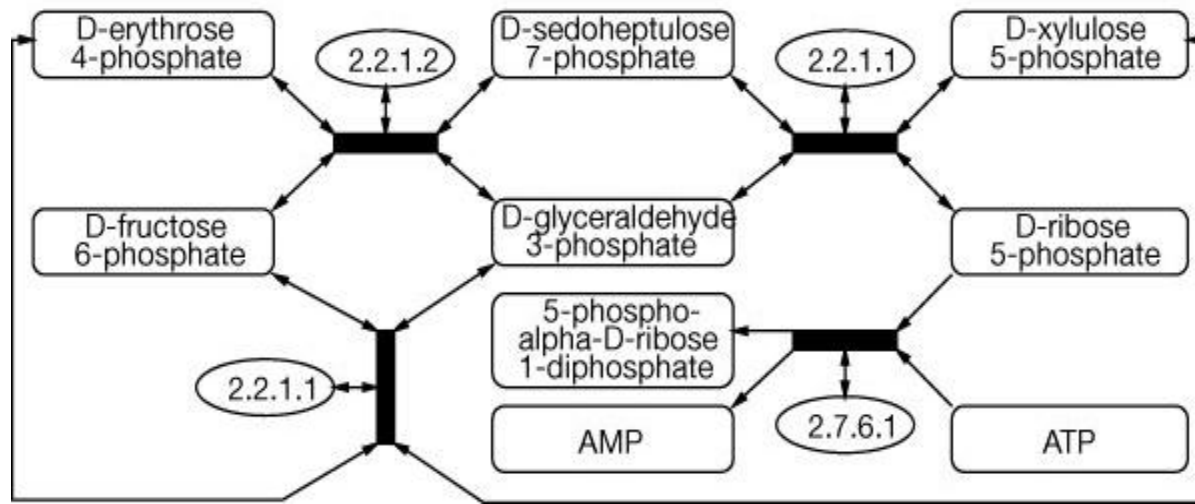


Enzymes shown in blue, co-enzymes (small molecules necessary for enzyme activity) in red. Double arrows mean reversible reactions. Reactants, products in black, box indicates that node appears in several locations.

Representation of chemical reactions+ regulation

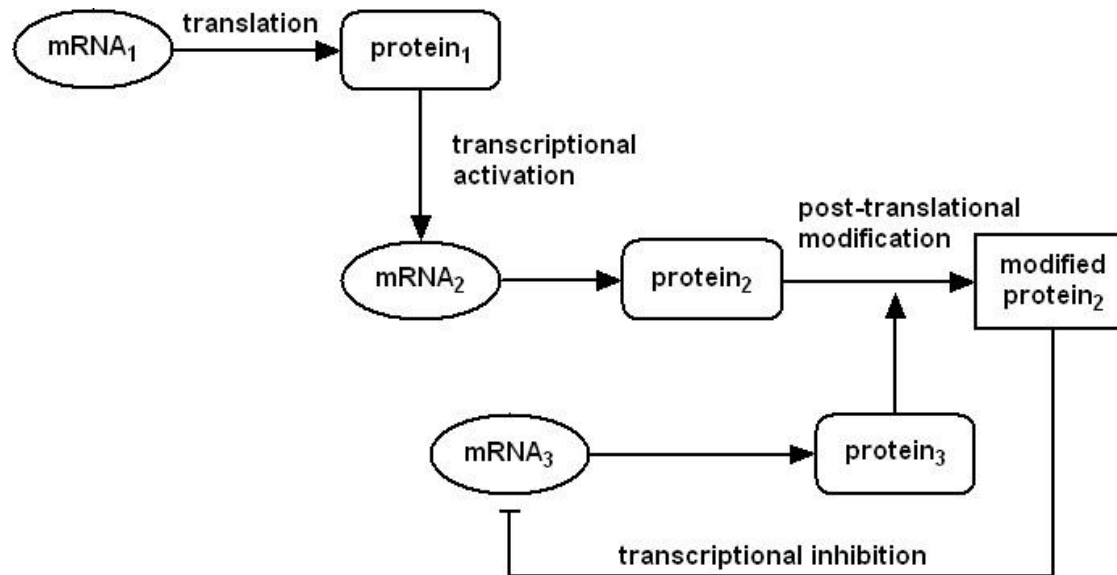


Tri-partite representation of metabolic network



- Node types:
 - Metabolites (substrates or products), open rectangles
 - No distinction between metabolites and coenzymes
 - Metabolite-enzyme complexes, black rectangles
 - Enzymes, open ovals
- Edges:
 - Substrate to complex or complex to product
 - Symmetrical edges between enzyme and complex

Gene regulatory networks



- nodes: mRNAs (ovals), proteins (boxes)
- edges: interaction or regulation
 - regulatory edges acting on edges – similar to catalysis
 - edges can be activating or inhibiting

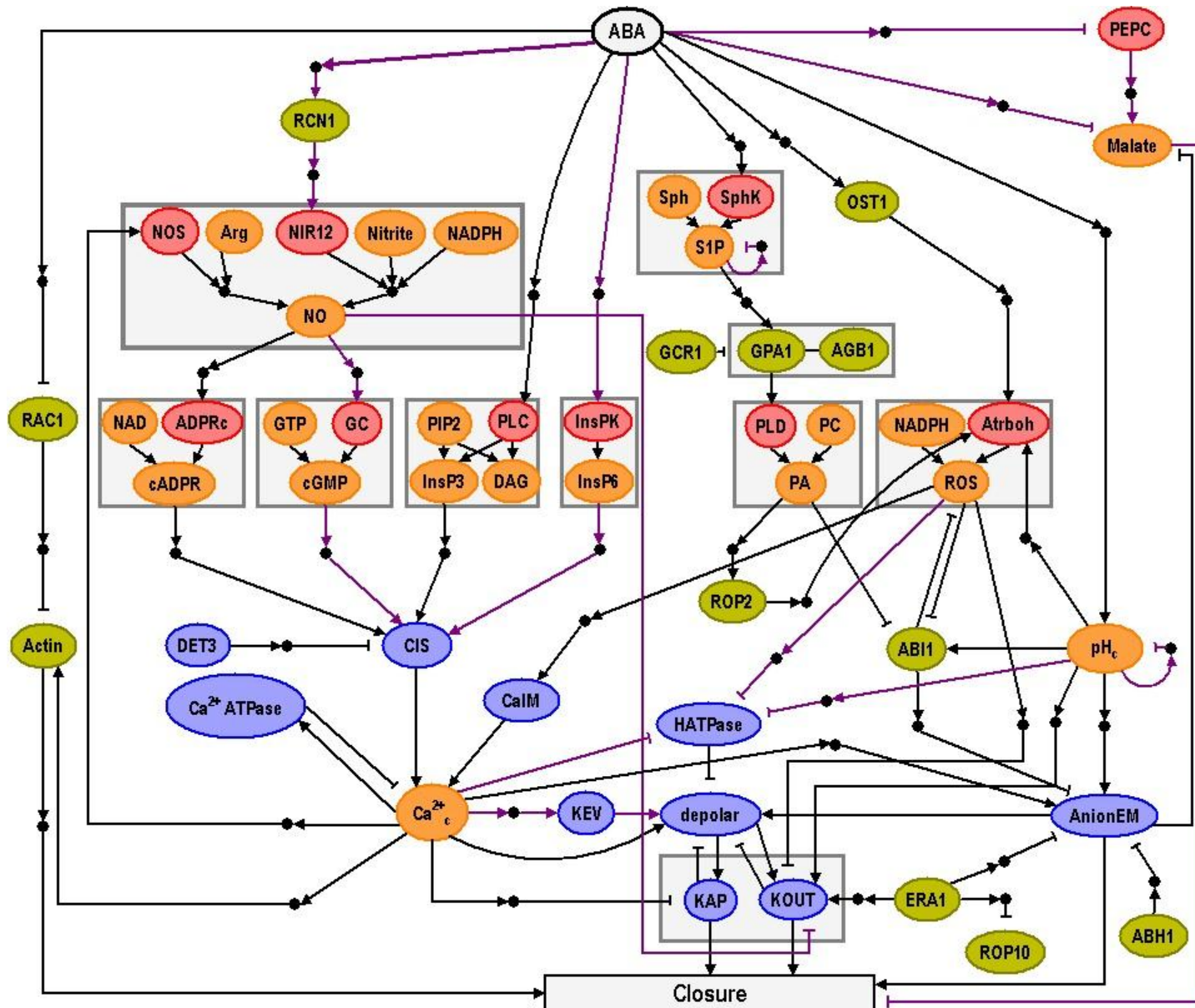
Often-used simplification: merge all gene products into a gene meta-node.

Q: What will the simplified network look like?

Ex. Draw a network corresponding to this verbal description of a signaling pathway.

- A protein ligand FASL binds to the receptor FAS. The interaction activates intracellular protein FADD, which in turn activates the proteolysis of procaspase-8, giving active caspase-8. Caspase-8 leads to the proteolytic activation of caspase-3, activating programmed cell death.

ABA signal transduction network



Red: enzymes
 Blue: transport
 Orange: small molecules
 Green: sign. transd. proteins
 Black points: unknown intermediary nodes

Li, Assmann, Albert, PLoS Biology 2006